Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
148344-176		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/008224	11.06.2004	13.06.2003

International Patent Classification (IPC) or national classification and IPC

Applicant

JAPAN AS REPRESENTED BY PRESIDENT OF NATIONAL CENTER FOR GERIATRICS AND GERONTOLOGY

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-17 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 15-18 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1,3,4,6,7,9,10,12-14 received by this Authority on 13.04.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1-4 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, nos. 2,5,8,11

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 17

because:

☒ the said international application, or the said claims Nos. 17
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 17 discloses a method for the treatment of Alzheimer's disease, which corresponds to a method for the treatment of the human body by means of surgery or therapy; therefore, claim 17 relates to a subject matter for which it is not necessary to carry out an international preliminary examination under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 17

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3, 4, 6, 7, 9, 10, 12-16, 18	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1, 3, 4, 6, 7, 9, 10, 12-16, 18	NO
Industrial applicability (IA)	Claims	1, 3, 4, 6, 7, 9, 10, 12-16, 18	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the international search report.

Document 5: WO 1999/27944 A1 (Athena Neurosciences, Inc.), 10 June 1999

Document 7: E. M. JOHNSTONE et al., Biochem. Biophys. Res. Commun., (1996), Vol. 220, pages 710 to 718

The following documents are newly cited by the International Preliminary Examining Authority.

Document 8: M. J. DURING et al., Science, (2000), Vol. 287, pages 1453 to 1460

Document 9: E. TARKOWSKI et al., Neurobiology of Ageing, (2002), Vol. 23, pages 237 to 243

(a)

Document 5 discloses immunogenic fragments (Aβ 1-12, Aβ 1-42 and the like) of the Aβ peptide (hereinafter referred to as the β-amyloid peptide), and discloses the feature of administering said immunogenic fragments and/or polypeptides that contain said immunogenic

fragments to an organism in order to treat Alzheimer's disease. Furthermore, document 1 also indicates that the administration of the β-amyloid peptide to a PDAPP mouse, which is a mouse model for Alzheimer's disease, resulted in the amelioration (the reduction) of the accumulation of amyloids in the cortex of the brain, which is one symptom of Alzheimer's disease (in particular, refer to fig. 12), and further suggests treating Alzheimer's disease by using an adeno-associated virus vector system in order to administer DNA that codes the aforementioned immunogenic fragments and/or DNA that codes the polypeptides which contain said immunogenic fragments to an organism via oral administration or the like (refer to page 21, lines 15 to 26 and page 21, line 35 to page 22, line 2 of the description).

(b)

Document 7 presents a method whereby a protein in which the signal peptide of the amyloid precursor protein (APP), which corresponds to amino acids 1 to 19 of the APP, has been fused upstream from the β-amyloid peptide (1-43) is expressed within a cell, whereafter the aforementioned β-amyloid peptide is secreted to the exterior of the cell in which it was expressed.

(c)

Document 8 presents a recombinant adeno-associated virus vector for introducing the gene that codes the N-methyl-D-asparate receptor (NMDAR), which is a protein that is expressed in the brain, into the *in vivo* intestinal cells of animals such as rats via oral administration; presents an oral vaccine for the

treatment of nervous system disorders that are associated with the NMDAR, which includes said recombinant adeno-associated virus vector as a constituent component; and presents a method for adjusting the recombinant adeno-associated virus vector so that it is possible to express the aforementioned gene within the aforementioned intestinal cells. Furthermore, document 8 suggests that the oral vaccine against the NMDAR proteins expressed in the brain, which includes said recombinant adeno-associated virus vector as a constituent component, is capable of inducing a humorous immunity within the body, but not of inducing cellular immunity.

(d)

Document 9 indicates that the concentration of TGF-β in the cerebrospinal fluid (CSF) of a group of Alzheimer's patients was high in comparison to that of a control group comprising healthy subjects (in particular, refer to fig. 2).

The inventions set forth in claims 1, 3, 4, 6, 7, 9, 10, 12 to 16 and 18 do not involve an inventive step in the light of document 5, document 7 and document 8.

The β-amyloid peptide that is disclosed in document 5 is a protein that is expressed in the brain; therein, document 5 suggests that said β-amyloid peptide can be used as an immunization source (a vaccine) for producing antibodies within an organism in order to treat Alzheimer's disease, and also suggests treating Alzheimer's disease by using an adeno-associated virus vector system in order to administer DNA that codes the β-amyloid peptide to an organism via oral administration

or the like. Furthermore, recombinant adeno-associated virus vectors for introducing a gene that codes a protein into the *in vivo* intestinal cells of animals via oral administration and oral vaccines that are capable of inducing a humorous immunity within the body but not cellular immunity, which comprise said adeno-associated virus vector vectors as constituent components, are well known as means whereby it is possible to employ another protein which is also expressed in the brain as a vaccine for the treatment of nervous system disorders, as indicated in document 8.

Meanwhile, in the written response the applicant asserts reasons to refute the existence of factors that would motivate a person skilled in the art to combine the inventions that are presented in document 5 and document 8, including the fact that the inventions set forth in the claims target Alzheimer's disease, which is a completely different type of disease from the nervous system disorders that are targeted by the vaccine that is presented in document 8, and the fact that that the antibody functions which are induced by the inventions are likewise different. However, even if the assertions by the applicant were accepted as being true, said assertions still are not considered to be sufficient to prevent a person skilled in the art from combining the inventions that are presented in document 5 and document 8.

Furthermore, it is known that in cases when genes that code proteins which are normally secreted by the original animal cell are introduced into another animal cell and expressed, the resulting expression products will also have a form that can be secreted; meanwhile,

although β-amyloid peptides are not secretion proteins, methods whereby a protein in which the signal peptide of the APP, which corresponds to amino acids 1 to 19 of the APP, has been fused upstream from the β-amyloid peptide is expressed within a cell in order to secrete the β-amyloid peptide to the outside of the cell in which it was expressed are well known, as disclosed in document 7.

Therefore, it would have been easy for a person skilled in the art to conceive of treating Alzheimer's disease by producing DNA that codes a fused protein in which the signal peptide of the APP has been bonded to the antigenic β-amyloid peptide (1-42) that is disclosed in document 5 or the like in the manner that is indicated in document 7; producing a recombinant adeno-associated virus vector by incorporating said produced DNA into an adeno-associated virus vector by means of the method that is presented in document 8; and then using said recombinant adeno-associated virus vector as an oral vaccine or other such drug for the treatment of Alzheimer's disease.

Furthermore, with regards to the effect whereby the administration of the vectors from the inventions that are set forth in the claims spurs the production of β-amyloid peptide antibodies and decreases the concentration of TGF-β1 in the blood serum, it would have been possible for a person skilled in the art to predict that the administration of an oral vaccine comprising the recombinant adeno-associated virus vector would cause the production of antibodies against the β-amyloid peptide in an organism, which would lead to the amelioration of the symptoms of Alzheimer's disease and thereby result in a decrease in the concentration of TGF-β within the CSF in

the light of the fact that the concentration of TGF-β in the cerebrospinal fluid (CSF) of a group of Alzheimer's patients was high in comparison to that of a control group comprising healthy subjects, as is indicated in document 9 for example, and the fact that the administration of the β-amyloid peptide to a mouse model for Alzheimer's disease caused the production of antibodies against the β-amyloid peptide within the mouse model and led to the amelioration of the symptoms of Alzheimer's disease, as disclosed in document 5. Furthermore, it is likely that a similar effect would have resulted even in cases when a β-amyloid peptide like that disclosed in document 5 itself is administered; therefore, the effect in question cannot be considered to be significant.

In the written response, the applicant asserts that it is possible to inhibit the deposition of amyloids in the cerebral blood vessels by administering the vectors from the inventions that are set forth in the claims. However, neither the description of the present application nor the written response includes specific disclosures including objective data which demonstrates that the inventions actually exhibit the effect in question, or which demonstrates that that said effect is superior to the effects that result from configurations wherein β-amyloid peptides are administered directly; therefore, said effect cannot be considered to be significant.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2004/050876 A [E,X]	17.06.2004	01.12.2003	29.11.2002

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☒ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*